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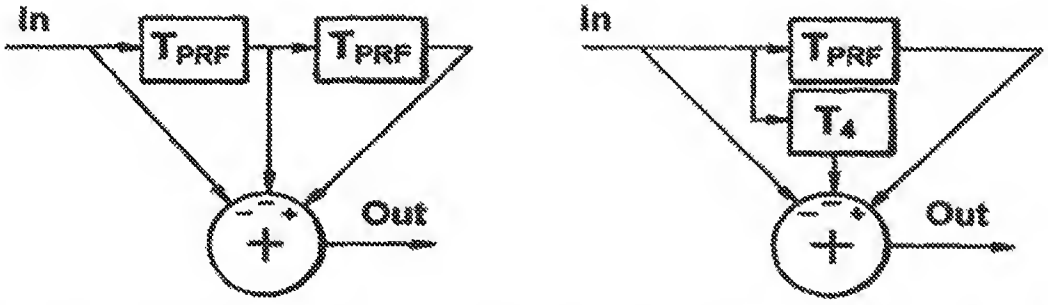
(54) Title: TECHNIQUES FOR IMPROVING ULTRASOUND CONTRAST RATIO



(57) Abstract: An ultrasound technique exploits differences in statefulness of response in order to distinguish between the objects of interest. The method comprises transmitting a primary excitation signal and one or more secondary excitation signals into a target medium receiving a corresponding plurality of responses from the target medium respectively resulting from the plurality of discrete excitation signals; and generating an output signal comprising the difference between the response to the primary excitation signal and either (i) the sum of the responses to the secondary excitation signals, or (ii) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response .

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TECHNIQUES FOR IMPROVING ULTRASOUND CONTRAST RATIO

The present invention relates to ultrasound detection and imaging techniques and in particular to methods for improving the contrast ratio between different structures within a target object, such as the human body.

Ultrasound contrast agent in the form of small gas bubbles (e.g. with an average diameter of 3 microns) is widely used to improve image quality in ultrasound scanning techniques practised on the human body. The gas bubbles are infused into a region of interest to increase the backscattered echoes from selected organs of interest. The gas bubbles are currently utilized mainly as tracers for non-invasive quantification of blood flow and many of them are now approved for left ventricular opacification and for enhanced endocardial border delineation. To extend the utility of ultrasound contrast for imaging, research has been actively focused in developing efficacious ultrasound contrast agents and new classes of contrast-specific imaging methods.

More stable contrast gas bubbles have recently been developed, designated as second- or third-generation contrast agents. The bubbles comprise a shell-encapsulated high molecular weight gas. The gas contained in the bubble plays the most important role in setting the lifetime and persistence of the contrast echo. The shell material controls the longevity of the bubble in addition to its linear and non-linear ultrasound scattering and absorption properties. The commitment of pharmaceutical companies for new ultrasound contrast bubble design and manufacturing techniques has been accompanied by a significant improvement in the way in which ultrasound imaging is performed. Specialized imaging methods have been developed to preferentially detect echoes from the contrast bubbles while reducing those from other structures, such as solid tissue. This is mainly attributed to the unique acoustical signatures of gas microbubbles, which differ from the signature of tissue.

One of these methods uses second harmonic scattering. Second harmonic-based techniques enhance the detection of contrast agent within many structures such as cardiac chambers. Differences between the response of gas microbubbles and tissue

to ultrasound irradiation are exploited. Soft tissues are known to be linear reflectors whereas contrast bubbles exhibit a nonlinear or harmonic behaviour when interacting with ultrasound waves. This property has been used to selectively image contrast bubbles and is now employed in commercial systems for transthoracic imaging and is termed 'contrast harmonic imaging'.

Although second harmonic imaging was the first technique that gave new capabilities to contrast imaging, differentiation between contrast agent and tissue, termed contrast-to-tissue ratio (CTR), is still in many situations cumbersome and contrast detection remains one of the main challenges, especially in capillaries. Reduced CTR is mainly caused by generation of harmonic energy from non-linear propagation effects in tissue, which hence obscures echoes from contrast bubbles.

From the fundamental imaging originally used in contrast echo techniques to second harmonic imaging, there have been several developed microbubble detection techniques. These include pulse inversion and power pulse inversion, power modulation, multi-pulse release imaging, subharmonic imaging and superharmonic imaging. All these detection strategies take advantage of the fact that microbubble response, and mainly its non-linear response, differs from the tissue response. In this way, the specific bubble component can be separated from the tissue component. Unfortunately, in many circumstances, present contrast imaging methods are still associated with various limitations that reduce their capability to discriminate tissue echoes from blood echoes. This results in a reduced contrast to tissue ratio (CTR).

The present invention is directed toward a technique for improving CTR, using a new multi-pulse contrast agent imaging method. The method described significantly attenuates the tissue component in a received echo signal while echoes from contrast agent pass relatively unsuppressed. Using the properties of a linear and stateless system we define a three pulse sequence that cancels perfectly when subtracted. Subsequently we show that changing the system from linear to non-linear does not change the cancellation property of the pulses. In addition, we show that in certain cases the three pulse sequence can be simplified to a two pulse sequence. The method is illustrated in a simulation study which shows high suppression of echoes

received from tissue and much less suppression of echoes received from a contrast agent bubble. The method is also illustrated in an *in-vitro* experiment which confirms the results found in the simulation study.

According to one aspect, the present invention provides a method of making ultrasound measurements on a target object comprising the steps of:

(a) transmitting a first excitation signal into a target medium;

(b) transmitting a second excitation signal into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a portion of the first excitation signal;

(c) receiving a first and a second response from the target medium, respectively corresponding to the first and second excitation signals; and

(d) generating an output signal comprising the difference between the first response and the sum of the second response and a time-shifted copy of the second response, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

The time shift may be substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

According to another aspect, the present invention provides a method of making ultrasound measurements on a target object comprising the steps of:

(a) transmitting a first excitation signal into a target medium;

(b) transmitting a second excitation signal into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a first portion of the first excitation signal;

(c) transmitting a third excitation signal into the target medium at a different time to the first and second excitation signals, the third excitation signal being substantially equal to a second portion of the first excitation signal;

(d) receiving a first, a second and a third response from the target medium, respectively corresponding to the first, the second and the third excitation signals; and

(e) generating an output signal comprising the difference between the first response and the sum of the second and third responses.

According to another aspect, the present invention provides a method of making ultrasound measurements on a target object comprising the steps of:

transmitting a plurality of discrete excitation signals into a target medium, the discrete excitation signals comprising a primary excitation signal and one or more secondary excitation signals;

receiving a corresponding plurality of responses from the target medium respectively resulting from the plurality of discrete excitation signals;

generating an output signal comprising the difference between the response to the primary excitation signal and either

(i) the sum of the responses to the secondary excitation signals, or

(ii) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being selected for appropriate alignment of the copies relative to the first response and the second response.

The time shift may be substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

According to another aspect, the present invention provides an apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving corresponding response signals from, a target medium;

an excitation signal generator for generating a first excitation signal and a second excitation signal at a different time to the first excitation signal, the second excitation signal being substantially equal to a portion of the first excitation signal; and

a signal processing device for receiving a first and a second response from the transducer, respectively corresponding to the first and second excitation signals and for generating an output signal comprising the difference between the first response

and the sum of the second response and a time-shifted copy of the second response, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

The time shift may be substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

According to another aspect, the present invention provides an apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving response signals from, a target medium;

an excitation signal generator for generating: a first excitation signal, a second excitation signal at a different time to the first excitation signal, the second excitation signal being substantially equal to a first portion of the first excitation signal, and a third excitation signal at a different time to the first and second excitation signals, the third excitation signal being substantially equal to a second portion of the first excitation signal; and

a signal processing device for receiving a first, a second and a third response from the transducer, respectively corresponding to the first, the second and the third excitation signals; and for generating an output signal comprising the difference between the first response and the sum of the second and third responses.

According to another aspect, the present invention provides an apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving excitation signals from, a target medium;

an excitation signal generator for generating a plurality of discrete excitation signals, the discrete excitation signals comprising a primary excitation signal and one or more secondary excitation signals;

a signal processor for receiving a corresponding plurality of responses from the transducer respectively resulting from the plurality of discrete excitation signals

and for generating an output signal comprising the difference between the response to the primary excitation signal and either

(i) the sum of the responses to the secondary excitation signals, or

(ii) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

The time shift may be substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

Embodiments of the invention will now be described, by way of example, and with reference to the accompanying drawings in which:

Figure 1 shows a three pulse combination that cancels perfectly when the first and second pulses are subtracted from the third pulse;

Figure 2 shows an ultrasound excitation burst sequence used for improved contrast agent to tissue discrimination;

Figure 3 shows two schematic diagrams of the processing steps for both a two burst sequence and a three burst sequence;

Figure 4 shows simulated pressure-time curves for non-linear ultrasound propagation at different excitation pressures and corresponding frequency domain information before and after processing;

Figure 5 shows simulated pressure-time curves for a single contrast agent bubble at different excitation pressures and corresponding frequency domain information before and after processing;

Figure 6 shows *in-vitro* results for tissue mimicking phantom and contrast agent in both time and frequency domain before and after processing; and

Figure 7 shows a schematic diagram of an apparatus suitable for implementing the invention.

Linear system theory defines a Linear Time-Invariant (LTI) system $h(t)$ as a system having the properties

$$a \cdot h(x_1(t)) + b \cdot h(x_2(t)) = h(a \cdot x_1(t) + b \cdot x_2(t)) \qquad \text{(eq. 1)}$$

and

$$x(t) \longrightarrow y(t)$$
$$x(t + \tau) \longrightarrow y(t + \tau), \qquad \text{(eqs. 2)}$$

in which $x(t)$, $x_1(t)$, and $x_2(t)$ are arbitrary input signals, a and b are arbitrary scaling constants, $y(t)$ is the response of the system to the input signal $x(t)$, and τ is an arbitrary time delay. Equation 1 defines linearity and is well known. Equation 2 defines time-invariance which states that a time shift on an input signal does not change the response of a system except for an equal time shift in the output signal.

Real-life systems are, in addition, necessarily causal which implies that the output of such a system cannot depend on input in the future. This can be expressed as

$$y(t) = h[x(t)] \text{ with } t \leq \tau, \qquad \text{(eq. 3)}$$

in which $h[\ ]$ indicates what values the system $h(t)$ uses to determine its output. Another property in system theory is the notion of 'state' or 'memory' in the system. The output of stateless or memoryless systems depends only on the current input and not on any input in the past. A memoryless system can hence be expressed as

$$y(t) = h[x(t)] \text{ with } t = \tau. \qquad \text{(eq. 4)}$$

An example of a stateless and causal LTI-system is an electrical resistor network. The notions of linearity and state in system theory are orthogonal concepts and therefore every combination of the two is possible.

In ultrasound, the complete imaging chain can be classified by these concepts as well. In the early days, the imaging system for tissue was considered to be a linear and time-variant system; linear because transducer and tissue scattering were considered

linear and time-variant because of movement in the imaged region, for example in the case of imaging the human heart.

More recently, harmonic imaging was introduced, which necessitated reclassification of an imaging system as a non-linear, time-variant system. Although the transducer was still considered linear, the medium was found to produce harmonics at higher ultrasound pressures and hence to be non-linear. Additionally, due to the high Pulse Repetition Frequencies (PRF's) currently used, the imaging system has essentially become time-invariant on the inter-pulse time-scale which is exploited in multi-pulse techniques like pulse inversion and power modulation.

As for state in the imaging system, it is clear that the imaging chain contains state information, which is most apparent from the delay between transmission of the pulse and reception of the response. The highly damped, large bandwidth transducers currently in use are well able to follow the electrical signal applied to them without showing much resonant behaviour and hence the state information they contain is limited. Linear propagation is stateful as the medium contains the propagating ultrasound pulse and delays the response for the time it travels from the transducer to a scatterer and back. However, this statefulness only amounts to a delay on the input signal and is easily discarded by working in retarded time

$$\tau = t - z / c_0,$$

in which z is the distance the excitation pulse has travelled and c_0 is the speed of sound in the medium.

From the KZK-equation that models non-linear propagation in tissue, we can deduce that the diffraction component in this equation is the only component that introduces state. Diffraction, however, is an effect that is not limited to non-linear propagation and is fully dependent on transducer geometry. Therefore, it is known in advance and can be taken into account when designing the transducer and the excitation. The non-linearity and the absorption components of the KZK-equation are stateless as their effect only depends on the instantaneous value of the pressure in the medium.

In summary, ultrasound imaging of tissue behaves on an inter-pulse time-scale as a non-linear and time-invariant system without any state in tissue except for a propagation delay.

The introduction of ultrasound contrast agents (UCA's) into the blood stream and tissue adds a new component to the imaging chain. UCA can be classified as a non-linear and stateful system, either time-invariant or time-variant on inter-pulse time-scale. Nonlinearity of a contrast agent bubble has long been recognised and used in various non-linear imaging techniques. The statefulness is easily appreciated from its resonant behaviour; a clear peak is visible in the response of a single contrast agent bubble when insonified at resonance frequency. Time-invariance or time-variance of a bubble system is dependent on the excitation pressure that is used to insonify the bubble. High excitation pressures change or destroy the bubble and hence the system becomes time-variant. If the pressure is low enough not to destroy or change the bubble at each firing (excitation pulse), the system becomes time-invariant on inter-pulse time-scale.

The system theoretic classification of tissue and contrast agent is compared in the table below:

	tissue	contrast agent
low pressure	• linear • time-invariant • stateless	• non-linear • time-invariant • stateful
high preasure	• non-linear • time-invariant • stateless	• non-linear • time-variant • stateful

We see that at low pressures both tissue and contrast agent are time-invariant, tissue is linear while contrast agent is non-linear, and tissue is stateless while contrast agent is stateful. The difference in linearity between tissue and contrast agent is exploited in techniques that are based on differences in non-linear responses, for example

harmonic imaging, pulse inversion and power modulation. These techniques use a signal processing approach to selectively extract the harmonic part from the received signal and hence detect the presence of contrast agent in tissue. Currently, no techniques are known to the inventors that are based on statefulness to detect the presence of contrast agent bubbles in tissue.

At high pressures, both tissue and contrast agent become non-linear. This property, therefore, cannot be used at high pressures to differentiate between bubbles and tissue. However, at higher pressures sufficient to cause the bubble to change or even to be destroyed, contrast agent becomes time-variant. This property is used in techniques like power Doppler and release burst imaging which use correlation based techniques to track the change in signature in the received signal from the contrast agent after a high power excitation pulse to disrupt the contrast agent. As with low power excitation, there are currently no techniques known to the inventors that exploit the difference in statefulness between tissue and contrast agent.

An important goal in contrast agent imaging has been the detection of contrast agent in perfused tissue. Currently most techniques are either based on the high non-linearity of a contrast agent bubble relative to tissue or the disruptability of the bubble. In both methods, however, tradeoffs have to be made when implemented in current ultrasound machinery.

Techniques based on non-linearity suffer from the non-linearity coming from tissue. As the non-linearity from tissue is confounded with the non-linearity from the contrast agent, it is very hard to untangle both signals and hence the quality of the image deteriorates from these contaminating tissue harmonics. In addition, the bandwidth of the transducer has to be divided to fit both transmission and reception bandwidth. The techniques based on disruption of the bubble cannot be used at high PRF's. As at each firing bubbles are destroyed, high PRF's would destroy all the bubbles before new ones arrive with the blood stream leaving no contrast agent in the imaged region. This effect severely limits the PRF and hence the image frame rate.

The present invention proposes a new signal processing approach that is based on the interaction between the non-linearity of a contrast agent bubble and its statefulness to selectively identify and suppress the response of tissue and improve the contrast to tissue ratio (CTR). Although the technique uses non-linearity, it does not need to record harmonics in the reflected signal which implies that transducers can be used at their optimal bandwidth. As it is mainly a low excitation pressure technique it does not disrupt the bubbles and can be used at high PRF.

Based on the response expected for a linear system as defined in equation 1 above, we define three excitation signals $x_1(t)$, $x_2(t)$ and $x_3(t)$, such that, for $t_1 < t_2 < t_3$

$$\begin{aligned} x_3(t) &= x_1(t) + x_2(t) && \text{for all } t \\ x_1(t) &= 0 && \text{for all } t \le t_1 \text{ and } t > t_2 \\ x_2(t) &= 0 && \text{for all } t \le t_2 \text{ and } t > t_3 \\ x_3(t) &= 0 && \text{for all } t \le t_1 \text{ and } t > t_3. \end{aligned} \qquad \text{(eqs. 5)}$$

Figure 1 shows an example of such signals, showing a three pulse combination that cancels perfectly when x_1 and x_2 are subtracted from x_3.

Using equation 1 it is clear that the response $y_3(t)$ of a linear system $h(t)$ to the input $x_3(t)$ equals the summed response of the system to the input signals $x_1(t)$ and $x_2(t)$, or

$$\begin{aligned} y_3(t) - y_1(t) - y_2(t) &= 0 && \text{for all } t \\ y_1(t) &= h(x_1(t)) \\ y_2(t) &= h(x_2(t)) \\ y_3(t) &= h(x_3(t)). \end{aligned} \qquad \text{(eqs. 6)}$$

For a non-linear system this is not necessarily the case, as equation 1 is not valid for non-linear systems. However, for a memoryless non-linear system for which $y(t) = 0$ if $x(t) = 0$, equations 6 are still valid since

$$\begin{aligned} x_3(t) &= x_1(t) && \text{for } t_1 < t \le t_2 \\ x_3(t) &= x_2(t) && \text{for } t_2 < t \le t_3 \end{aligned}$$

$$x_3(t) = 0 \qquad \text{for all } t \leq t_1 \text{ and } t > t_3 \qquad \text{(eqs. 7)}$$

Using equation 4 on these inputs for a memoryless non-linear system $n(t)$, it is clear that

$$y_3(t) = n(x_3(t)) = n(x_1(t)) = y_1(t) \text{ for } t_1 < t \leq t_2$$
$$y_3(t) = n(x_3(t)) = n(x_2(t)) = y_2(t) \text{ for } t_2 < t \leq t_3$$
$$y_3(t) = 0 \qquad \text{for } t \leq t_1 \text{ and } t > t_3. \qquad \text{(eqs. 8)}$$

Concatenating time intervals and noting that we assumed $y(t) = 0$ if $x(t) = 0$, it is proven that equations 6 are valid for non-linear memoryless systems when using input signals according to equations 5.

Applying this approach to ultrasound imaging with contrast agents, the power of this technique becomes clear. Our aim is to suppress the signal coming from tissue to increase the relative contribution of the contrast agent signal and hence increase the CTR. As is clear from the table above, tissue reacts either linearly or non-linearly depending on the applied ultrasound pressure. Suppression of the tissue signal in the linear case is possible by using any combination of three excitation signals so that $x_3(t) = x_1(t) + x_2(t)$ is true.

For higher ultrasound pressures, when tissue starts to react non-linearly, this approach does not necessarily obtain full cancellation of the tissue signal anymore. However, as tissue remains stateless in both excitation conditions, the signal from tissue can be cancelled by using a pulse sequence as defined in equations 5.

Contrast agents react differently. A contrast agent bubble is non-linear for both low and high power excitations and, unlike tissue, is stateful. This implies that equations 6 and 7 do not hold for reflections coming from contrast agent bubbles. Therefore, full cancellation of contrast agent signal will not occur and a residual contrast agent signal will remain. When this residual signal is large enough to be detected, an increase in CTR can be obtained without destroying the bubble and/or without using harmonic components from the response.

A physical explanation of the residual signal is an interaction between the non-linearity and the statefulness of the contrast agent bubble. Signals from linear systems always cancel, irrespective of any state in the system; for non-linear systems, the signals only cancel when the system is stateless.

For a stateful system, the output at time t does not only depend on the input at time t, but also on the input before t. In figure 1, we see that the last half of signal $x_3(t)$ equals $x_2(t)$. In $x_3(t)$, however, there is a signal before that last half, that is absent in $x_2(t)$. When a stateless system responds to $x_3(t)$ as input, the last half of the response will be equal to the response from $x_2(t)$ as it does not matter what has happened before current time for a stateless system. When the system is stateful, it does matter what has happened before and hence the output for the last half will differ. Signal $x_1(t)$ is used to calculate the response of the first half of $x_3(t)$, which for both a stateless and stateful system should match perfectly as all real-life systems are causal and cannot look into the future.

When implementing this technique into real hardware a few issues are encountered.

Firstly, transducers have finite bandwidth and hence cannot exactly reproduce the non-overlapping waveforms. This issue only becomes important when imaging tissue in a nonlinear regime, i.e. at high ultrasound pressures. In a linear regime, the waveforms still fully cancel as only the linearity property is used and the distortions introduced at the front and the back of the waveform by the finite bandwidth of the transducer fully cancel. In the nonlinear regime, some residual signal is expected from the tissue which will confound with the residual signal from the contrast agent and decrease the obtained CTR in the image. However, as this is a fixed and fully transducer-dependent effect, it can be compensated for in the pulser (excitation drive circuits) to minimise the overlap in the signals to limited transducer bandwidth.

Secondly, when using a pulse sequence as shown in figure 1, a pulsing scheme which transmits only two pulses will suffice. As the only difference between $x_1(t)$ and $x_2(t)$ is a time delay of exactly four cycles and we consider the system to be time-invariant,

we can use $x_1(t)$ to generate both $y_1(t)$ and $y_2(t)$ by delaying $y_1(t)$ four cycles to obtain $y_2(t)$. Using fewer transmitted pulses will improve frame rate and make it easier to compare this technique with pulse-inversion and power-modulation techniques which are both based on two transmit firings.

To confirm the feasibility of the approach described above, we performed simulations of nonlinear propagation and a single contrast agent bubble. Additionally, the simulation results were validated with *in-vitro* measurements of a phantom and a low concentration dilution of an experimental contrast agent. For the simulations and the measurements, an excitation sequence was defined as shown in figure 2.

Figure 2 shows an exemplary three-burst excitation sequence that has the desired cancellation property in both the simulation study and *in-vitro* measurements.

The sequence consists of an eight-cycle burst at 2 MHz, followed by two four-cycle bursts at 2 MHz. All bursts have equal amplitude and are spaced T_{PRP} apart with an additional delay of four cycles (T4) for the last four-cycle burst. A two-burst excitation sequence can alternatively be used derived from the three-burst excitation sequence by omitting the last four-cycle burst. After recording the responses to the three-burst excitation sequence, a processing step is needed to obtain the tissue suppression result.

The processing step for the three-burst scheme is depicted in figure 3(a). The two four-cycle bursts are appropriately delayed and subtracted from the eight-cycle burst. For the two-burst excitation schema, the processing is depicted in Fig. 2.3(b). Here, the single four-cycle burst is delayed for four cycles (T_4) and both the original four-cycle burst and the delayed version are subtracted from the eight-cycle burst.

Thus, in a general sense, it will be noted that the three-burst scheme provides the steps of: (a) transmitting a first excitation signal (e.g. $x_3(t)$, or T_8) into a target medium; (b) transmitting a second excitation signal (e.g. $x_1(t)$, or T_4) into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a first portion of the first excitation signal; (c) transmitting a

third excitation signal (e.g. $x_2(t)$, or T_4 again) into the target medium at a different time to the first and second excitation signals, the third excitation signal being substantially equal to a second portion of the first excitation signal; (d) receiving a first, a second and a third response (e.g. $y_3(t)$, $y_1(t)$ and $y_2(t)$) from the target medium, respectively corresponding to or resulting from the first, the second and the third excitation signals; and (e) generating an output signal (e.g. 'Out', figure 3(b)) comprising the difference between the first response ($y_3(t)$) and the sum of the second and third responses ($y_1(t) + y_2(t)$).

Further, in a general sense, it will be noted that the two-burst scheme provides the steps of: (a) transmitting a first excitation signal (e.g. $x_2(t)$, or T_3) into a target medium; (b) transmitting a second excitation signal (e.g. $x_1(t)$, or T_4) into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a portion of the first excitation signal; (c) receiving a first and a second response (e.g. $y_2(t)$ and $y_1(t)$) from the target medium, respectively corresponding to or resulting from the first and second excitation signals; and (d) generating an output signal (e.g. 'Out', figure 3(a)) comprising the difference between the first response ($y_2(t)$) and the sum of the second response (e.g. $y_1(t)$) and a time-shifted copy of the second response (e.g. $y_1(t)$), the time shift being substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal. Preferably, the second excitation signal is transmitted subsequent to the first excitation signal.

A number of other observations about the general techniques are appropriate at this point.

While it is desirable that the second and/or third excitation signals is/are substantially equal to a portion of the first excitation signal, to simplify subsequent processing, this 'equality' refers to the frequency component or components of the excitation signals and not necessarily to the amplitudes. Thus, the second and/or third excitation signals may be amplitude scaled versions of the portions of the first excitation signal. In this case, it may be necessary to perform amplification or scaling to normalise the

response signals. Still further, the second and third excitation signals may have different frequencies.

The expression 'scaling' of the signals may also be used to encompass inversion, e.g. scaling by a factor of –1. Thus, any one of the first, second or third excitation signals may be inverted, provided that appropriate compensation is made during the response signal processing.

The principles of the invention are also extendable to more than the number of pulses indicated in the illustrated embodiments above. For the three pulse scheme, it will be noted that further excitation signals (after the second and third excitation signals) may be transmitted into the target medium, each further excitation signal substantially equal to a portion of the first excitation signal. This generates further responses from the target medium, each further response corresponding to one of the further excitation signals. The output signal is then generated as a difference between the first response and a sum of the second, third and further responses. Generally speaking, the sum of the second, third and subsequent excitation bursts should be equal to the first excitation burst.

For the two pulse scheme, it will be noted that the second excitation signal need not be exactly half of the first excitation signal. More generally, the second excitation signal may be a fraction (i.e. 1/N *th* portion) of the first excitation signal. In this case, the output signal is then generated as a difference between the first response and the sum of the second response and (N–1) time-shifted copies of the second response.

The first and the second excitation signals are selected such that the difference between the first excitation signal and the sum of N second excitation signals suitably time-displaced is substantially zero.

Thus, in a general sense, step (d), as defined earlier, may be modified to comprise generating an output signal (e.g. 'Out', figure 3(a)) comprising the difference between the first response ($y_3(t)$) and the sum of the second response (e.g. $y_1(t)$) and a number N-1 of time-shifted copies of the second response (e.g. $y_1(t)$), the time shifts

for each of the N-1 copies being from 1/N times the duration of the first excitation signal to (N-1)/N times the duration of the first excitation signal, referenced against the start of the first excitation signal to ensure appropriate alignment.

Stated another way, the time shifts for each of the copies are selected for appropriate alignment of the or each copy relative to the first response and the second response, e.g. substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

Further, it is noted that the order of the first, second and third excitation signals may be changed. Providing that the responses are suitably delayed for correct relative alignment prior to summing, there is no necessity for the full, or 'primary' excitation signal $x_3(t)$ to be first; one or more of the partial, or 'secondary' excitation signals $x_1(t)$ or $x_2(t)$ may be transmitted first.

Thus, in a still more general sense, the technique may comprise transmitting a plurality of discrete excitation signals into the target medium, in which the discrete excitation signals comprise a primary excitation signal and one or more secondary excitation signals; receiving a corresponding plurality of responses from the target medium respectively corresponding to the plurality of discrete excitation signals; and generating an output signal comprising the difference between the response to the primary excitation signal and either (a) the sum of the responses to the secondary excitation signals, or (b) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being substantially equal to a time gap between the primary and secondary excitation signals.

Simulation

The effects of non-linear propagation in tissue were simulated by solving the KZK-equation. A computer program was written in Matlab (The Mathworks, Inc., Natick, MA, USA) and C to solve the parabolic wave equation in time domain for arbitrary excitations. The program was used to calculate the on-axis response at the focus of a 25 mm diameter focussed single element transducer. The focal depth of the

transducer was 75 mm; the coefficient of absorption and the coefficient of non-linearity (B / A) were set at 4.3×10^{-6} $m^2.s^{-1}$ and 2.5, respectively. The excitation was as defined in figure 2 and scaled to produce approximately 50 kPa, 100 kPa, 200 kPa, and 500 kPa peak pressure at the focus. At 2 MHz, these pressures correspond to mechanical indices (MI's) of 0.035, 0.07, 0.14 and 0.35 of which the first two are in the range used in non-destructive contrast agent imaging. The pressure waveforms resulting from the simulation were appropriately delayed and subtracted according to figure 3(a) to obtain the suppressed tissue signal.

The response of a single contrast agent bubble was calculated from a modified RPNNP differential equation, named after its developers Rayleigh, Plesset, Noltingk, Neppiras and Poritski, using Simulink and Matlab. A single contrast agent bubble with 2.75 micron radius and a resonance frequency of 2.0 MHz was excited with the burst sequence as defined in figure 2 scaled to 10 kPa, 20 kPa, 50 kPa and 100 kPa peak pressure. By using these low peak pressures we expect to be in the range which does not disrupt the contrast agent and hence obtain simulation results valid for non-destructive contrast agent imaging. The shell property parameters were set according to the shell properties of commercially available contrast agent. The simulated pressure waveforms at some distance from the bubble were delayed and subtracted according to figure 3(a) to obtain the resulting bubble signal. Using the simulated non-linear propagation and contrast agent signals we evaluated the performance of the new approach in both time and frequency domain.

Measurements

For evaluation of the approach, we performed an *in-vitro* experiment in which we processed ultrasound traces recorded from either an agar-agar, tissue mimicking phantom or a container with a low concentration of contrast agent. The phantom consisted of 3% agar-agar with 0.4% carborundum to mimic tissue scattering. The contrast agent was a 1:5000 dilution of BR-14 (Bracco Research SA, Geneva, Switzerland) in an acoustically transparent container.

With reference to figure 7, the evaluation may be performed in a water tank containing gas saturated water in which either the phantom or the contrast agent (or

any other target object 70) is placed at the focus of a 2.25 MHz single element broadband transducer 72 (e.g. PZT, diameter 32 mm, 75 mm focal length (Panametrics, Waltham, MA, USA)) mounted at the side of the water tank. The excitation sequence may be generated with an arbitrary waveform generator 74 (e.g. LW420A, LeCroy, Chestnut Ridge, NY, USA), attenuated with a variable attenuator 75 (e.g. 355C/D, HP, Palo Alto, CA, USA), and amplified by a 50 dB linear power amplifier 76 (e.g. 2100L, ENI, Rochester, USA).

To keep bubble disruption to a minimum, the maximum MI may be limited, e.g. MI < 0.1. The echo signal 77 may be recorded with an 8-bit digital oscilloscope (9400A, LeCroy, Chestnut Ridge, NY, USA) or other digital recording device 78 and processed off-line using a suitable processing device 80, e.g. an IBM-compatible PC.

To increase the accuracy of the timing and to obtain a measurement of the decorrelation due to bubble movement, the excitation sequence may be slightly modified by removing the T_4 delay of the last four-cycle burst. In the example, the processing scheme used was the two burst scheme depicted in Fig. 2.3(b). TPRF was set to 160 microseconds. To lower the noise level in the phantom measurements, 1000 traces were averaged. As contrast agent bubbles are moving around and hence the traces are not time-invariant, this was not appropriate for the contrast agent traces and non-averaged traces were used for processing. Therefore, the noise level in the contrast agent measurements is higher than the noise level in the phantom measurements.

Results

The results from the non-linear and contrast agent bubble simulations are depicted in figures 4 and 5. Figure 4 shows simulated pressure-time curves for non-linear propagation with the KZK-equation at several excitation pressures. The top three rows depict, in the time domain, the signals before processing. The fourth row shows, in the time domain, the resulting signal after processing. The bottom row shows the signals before (solid line) and after (broken line) processing, in the frequency domain. Figure 5 shows simulated pressure-time curves for a single contrast agent bubble using a modified RPNNP-equation at several excitation

pressures. The top three rows depict, in the time domain, the signals before processing. The fourth row shows, in the time domain, the resulting signal after processing. The bottom row the signals before (solid line) and after (broken line) processing, in frequency domain.

Both figures 4 and 5 show in columns the signals that occur at several points in the processing chain for the previously defined peak pressures. The upper three rows show the results from the Matlab simulation programs with each graph normalised to the peak pressure at the top of the column in which it resides and aligned in time for the subtraction of the two four-cycle bursts from the eight-cycle burst. It is clear that the responses from the two four cycle bursts differ only by a time shift. The fourth row shows the result from the subtraction.

Although both for non-linear propagation and for a contrast agent bubble the amplitude of the residual signal increases for increasing peak pressure, the scaling of the figures is made different for visibility of the residual signal. For non-linear propagation in figure 4, the vertical axis is scaled to 1/10 of the vertical scale of the graphs above; for the contrast agent bubble in figure 5, the vertical axis is scaled to only 1/2 of the vertical scale above.

Another clear difference between the residual signals is their length in time and periodicity. The main part of the residual signal from non-linear propagation is very bounded in time; it consist of a single cycle that, in addition, has a frequency that is much higher than the frequency of the excitation. On the other hand, the contrast bubble residual signal is much longer in time and clearly shows a fundamental frequency that is equal to the frequency of the excitation.

Finally, the last row shows the Fourier transforms of the four cycle response from the second row and the residual signal from the fourth row. Additionally, the graphs are not normalised and hence are comparable between columns. For non-linear propagation we see large suppression of the non-linear propagation signal. At the fundamental at 2 MHz the amount of suppression ranges from approximately 80 dB for the 50 kPa signal to 50 dB for the 500 kPa signal. In addition, the frequency

spectrum of the residual signal is almost flat and shows no clear fundamental and harmonic frequency components. For the contrast agent bubble we see suppression of the reflected signal as well, but to a much lesser extent. The fundamental is suppressed approximately 40 dB at 10 kPa excitation and 20 dB at 100 kPa excitation. At the second harmonic, the lack of suppression is more even clear as in all cases the suppression is only a few dB's. In addition, the residual signal shows the fundamental frequency component and the higher harmonics.

The results from the *in-vitro* experiments are in accordance with the simulation results and are shown in figure 6. Figure 6 shows *in-vitro* measurements of a tissue mimicking phantom (left) and a contrast agent suspension (right). The top and bottom figures depict the measured echo signals before processing in time and frequency domain (solid line), respectively. The bottom figures depict the processed signals in time and frequency domain (broken line), showing significant suppression of the echo signal from the tissue mimicking phantom.

The two columns show the signals as obtained from the tissue mimicking phantom and the contrast agent dilution. The top row shows the received signal from the four-cycle burst, the middle row the residual signal after processing and the bottom row the Fourier transforms of the signals above. The suppression for the phantom is clearly seen in the time signal which contains mainly noise after processing as well as in the Fourier transform graph which nicely shows the suppression of the received signal in the bandwidth of the transducer. At the fundamental and second harmonic we see suppression of approximately 25 dB and 15 dB respectively. Comparing this with the received signal from the contrast agent dilution, we see a slight decrease in average amplitude in the time signal after processing. In the Fourier transform graph a slight suppression is visible around the fundamental; at other frequencies the curves overlap.

In summary, detection of contrast agent in perfused tissue has been an important research topic for many years. The methods that are currently available are either based on the high nonlinear scattering of a contrast agent bubble or destruction of the contrast agent. The most important representatives of the first method are harmonic

imaging, power modulation and pulse inversion. All three techniques use a spectral filtering approach to extract that part of the spectrum in which the received signal shows the largest difference between tissue and contrast agent. A drawback of these techniques is that the transducer bandwidth is implicitly or explicitly divided into a transmission sub-band and a reception sub-band and therefore not optimally used. Differences in system theoretic behaviour of non-linear propagation and contrast agent are not used with these techniques. The maximum obtainable CTR is hence limited by differences in non-linearity.

The approach of the present invention uses the difference in system behaviour between tissue and bubbles to detect the contrast agent and suppress the tissue signal. The simulation results and the measurements clearly show the ability to untangle both signals and improve the contrast to tissue ratio above the CTR that is inherent in the received signal. For example, at 100 kPa simulation results show at the fundamental a suppression of 70 dB for non-linear propagation response and 18 dB for the contrast agent bubble response; an increase of approximately 52 dB in CTR after processing the signals with the new approach. For harmonics the effect are similar. For the non-linear propagation signal we find significant suppression while the bubble signal is hardly suppressed. In figure 5 we even see at 100 kPa an increase of the fourth harmonic after processing. Although the experimental setup was not optimised for this approach, we found significant suppression of the phantom signal while the contrast agent signal was hardly suppressed. Figure 6 shows an approximate increase of 20 dB in CTR at the fundamental and 15 dB at the second harmonic. As we used an 8-4-4 cycle pulsing scheme in the experiments, it is possible check for decorrelation due to movement of the contrast agent by subtraction the responses of the two four cycle bursts. No decorrelation due to bubble movements was found and hence the residual signal can be fully subscribed to be caused by statefulness of the contrast agent.

Though the present method is based on interaction between non-linearity and statefulness, the operations which implement the processing are linear operations. This implies that most techniques that are in use in ultrasound applications can still be applied. For example, pulse inversion and power modulation can still be applied; at a

cost, however, of further reducing frame rate. Furthermore, as pulse inversion is already based on subtraction of carefully aligned traces from different firings, much of the signal processing infrastructure that is necessary to implement this technique is already available.

Therefore, adding the present technique to current ultrasound scanners is well possible without large investments in hardware. Although the present technique is designed for non-destructive imaging, destruction of contrast agent will not immediately cancel its applicability. As destruction of the contrast agent means decorrelation of the contrast agent signals, it will show up as an increase in the residual signal after processing. However, as the decorrelation prevents full cancellation of the first four cycles of the eight-cycle burst, the will be a loss in resolution in the contrast agent signal. On the other hand, as the technique is based on suppression of signals, the noise floor of the imaging system becomes the limit of suppression.

Extensions of the described techniques can readily be implemented. For example, any combination of two, not necessarily equal, pulses which do not overlap in time can be used. The two pulses can differ in phase amplitude, frequency or phase or a combination of these. The third pulse is then derived by adding the former two. Another extension is the use of harmonics instead of the fundamental as described here.

The invention provides a new processing method that highly suppresses echoes from tissue while echoes from contrast agent pass relatively unchanged. As the method is fully linear, it can be added as a front-end to existing processing schemes to give large improvements in CTR with destroying the contrast agent.

Other embodiments are intentionally within the scope of the accompanying claims.

CLAIMS

1. A method of making ultrasound measurements on a target object comprising the steps of:

(a) transmitting a first excitation signal into a target medium;

(b) transmitting a second excitation signal into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a portion of the first excitation signal;

(c) receiving a first and a second response from the target medium, respectively corresponding to the first and second excitation signals; and

(d) generating an output signal comprising the difference between the first response and the sum of the second response and a time-shifted copy of the second response, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

2. The method of claim 1 in which the second excitation signal is a 1/N *th* portion of the first excitation signal, and in which step (d) comprises generating the output signal as the difference between the first response and the sum of the second response and (N–1) time-shifted copies of the second response.

3. The method of claim 1 in which the second excitation signal is an amplitude scaled version of the first excitation signal.

4. The method of claim 1, claim 2 or claim 3 in which step (d) further includes the step of amplitude scaling one or more of the first and second responses prior to calculating said difference.

5. The method of claim 1 in which the first excitation signal is substantially equal to an amplitude scaled sum of the second excitation signal and a time shifted copy of the second excitation signal.

6. The method of claim 5 in which the amplitude scaling factor is unity.

7. The method of claim 5 in which the amplitude scaling factor is –1.

8. The method of claim 1 in which the first excitation signal is a burst of n cycles of frequency *f* and the second excitation signal is a burst of n/2 cycles of frequency *f*.

9. The method of claim 2 in which the first excitation signal is a burst of n cycles of frequency *f* and the second excitation signal is a burst of n/N cycles of frequency *f*.

10. The method of claim 1 in which the first and second excitation signals are selected such that the difference between the first excitation signal and the sum of the second excitation signal and a time-displaced version of the second excitation signal is substantially zero.

11. The method of claim 1 in which the time shift is substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

12. A method of making ultrasound measurements on a target object comprising the steps of:

(a) transmitting a first excitation signal into a target medium;

(b) transmitting a second excitation signal into the target medium at a different time to the first excitation signal, the second excitation signal being substantially equal to a first portion of the first excitation signal;

(c) transmitting a third excitation signal into the target medium at a different time to the first and second excitation signals, the third excitation signal being substantially equal to a second portion of the first excitation signal;

(d) receiving a first, a second and a third response from the target medium, respectively corresponding to the first, the second and the third excitation signals; and

(e) generating an output signal comprising the difference between the first response and the sum of the second and third responses.

13. The method of claim 12 in which:

step (b) includes transmitting further excitation signals, each separated in time from the other excitation signals and each substantially equal to a portion of the first excitation signal, into the target medium, and

step (c) includes receiving further responses from the target medium, each further response corresponding to one of the further excitation signals; and

step (d) comprises generating the output signal as a difference between the first response and a sum of the second, third and further responses.

14. The method of claim 12 in which the second and/or third excitation signal is an amplitude scaled version of the first excitation signal.

15. The method of claim 12, claim 13 or claim 14 in which step (d) further includes the step of amplitude scaling one or more of the first, second and third responses prior to calculating said difference.

16. The method of claim 12 in which the first excitation signal is substantially equal to an amplitude scaled sum of the second and third excitation signals.

17. The method of claim 16 in which the amplitude scaling factor is unity.

18. The method of claim 16 in which the amplitude scaling factor is –1.

19. The method of claim 12 in which the first excitation signal is a burst of n cycles of frequency f and the second and third excitation signals are each a burst of n/2 cycles of frequency f.

20. The method of claim 12 in which the first, second and third excitation signals are selected such that the difference between the first excitation signal and the sum of the second excitation signal and the third excitation signal is substantially zero.

21. The method of claim 12 in which the frequency of the second excitation signal is different to the frequency of the third excitation signal.

22. A method of making ultrasound measurements on a target object comprising the steps of:

transmitting a plurality of discrete excitation signals into a target medium, the discrete excitation signals comprising a primary excitation signal and one or more secondary excitation signals;

receiving a corresponding plurality of responses from the target medium respectively resulting from the plurality of discrete excitation signals;

generating an output signal comprising the difference between the response to the primary excitation signal and either

(i) the sum of the responses to the secondary excitation signals, or

(ii) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

23. The method of claim 22 in which the time shift is substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

24. Apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving corresponding response signals from, a target medium;

an excitation signal generator for generating a first excitation signal and a second excitation signal at a different time to the first excitation signal, the second excitation signal being substantially equal to a portion of the first excitation signal;

a signal processing device for receiving a first and a second response from the transducer, respectively corresponding to the first and second excitation signals and for generating an output signal comprising the difference between the first response and the sum of the second response and a time-shifted copy of the second response, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

25. The apparatus of claim 24 in which the time shift is substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

26. Apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving response signals from, a target medium;

an excitation signal generator for generating: a first excitation signal, a second excitation signal at a different time to the first excitation signal, the second excitation signal being substantially equal to a first portion of the first excitation signal, and a third excitation signal at a different time to the first and second excitation signals, the third excitation signal being substantially equal to a second portion of the first excitation signal;

a signal processing device for receiving a first, a second and a third response from the transducer, respectively corresponding to the first, the second and the third excitation signals; and for generating an output signal comprising the difference between the first response and the sum of the second and third responses.

27. Apparatus for making ultrasound measurements on a target object comprising:

a transducer for transmitting excitation signals into, and receiving excitation signals from, a target medium;

an excitation signal generator for generating a plurality of discrete excitation signals, the discrete excitation signals comprising a primary excitation signal and one or more secondary excitation signals;

a signal processor for receiving a corresponding plurality of responses from the transducer respectively resulting from the plurality of discrete excitation signals and for generating an output signal comprising the difference between the response to the primary excitation signal and either

(i) the sum of the responses to the secondary excitation signals, or

(ii) the sum of the response to a single secondary excitation signal and one or more time-shifted copies of the response to the single secondary excitation signal, the time shift being selected for appropriate alignment of the copy relative to the first response and the second response.

28. The apparatus of claim 27 in which the time shift is substantially equal to the difference between the duration of the first excitation signal and the duration of the second excitation signal or a fraction thereof.

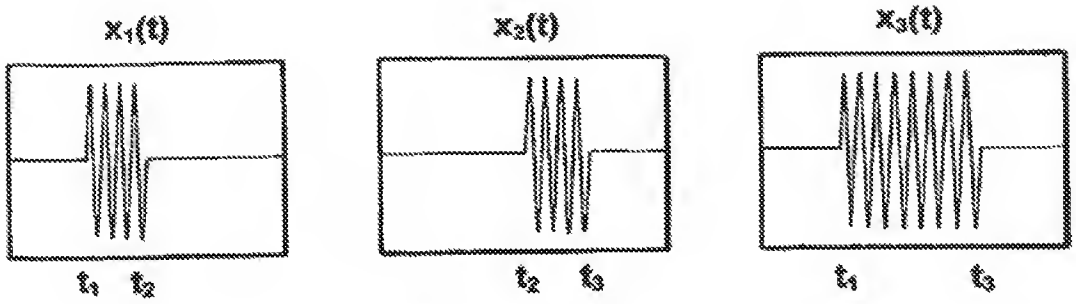


Fig. 1

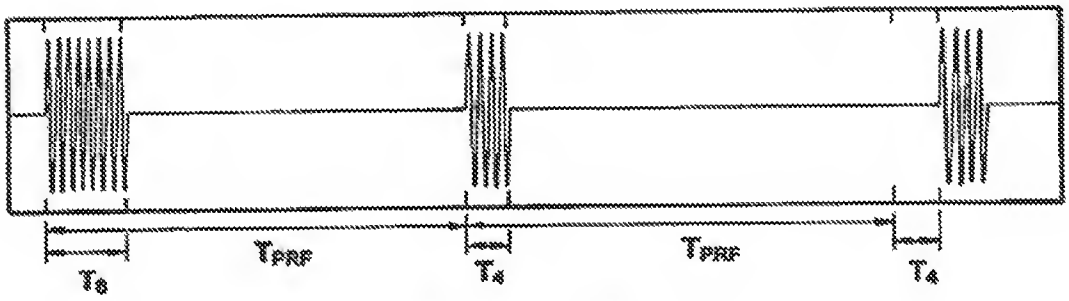


Fig. 2

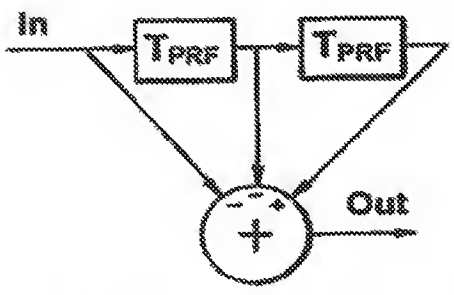


Fig. 3(a)

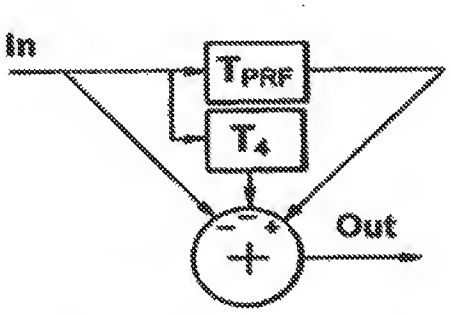
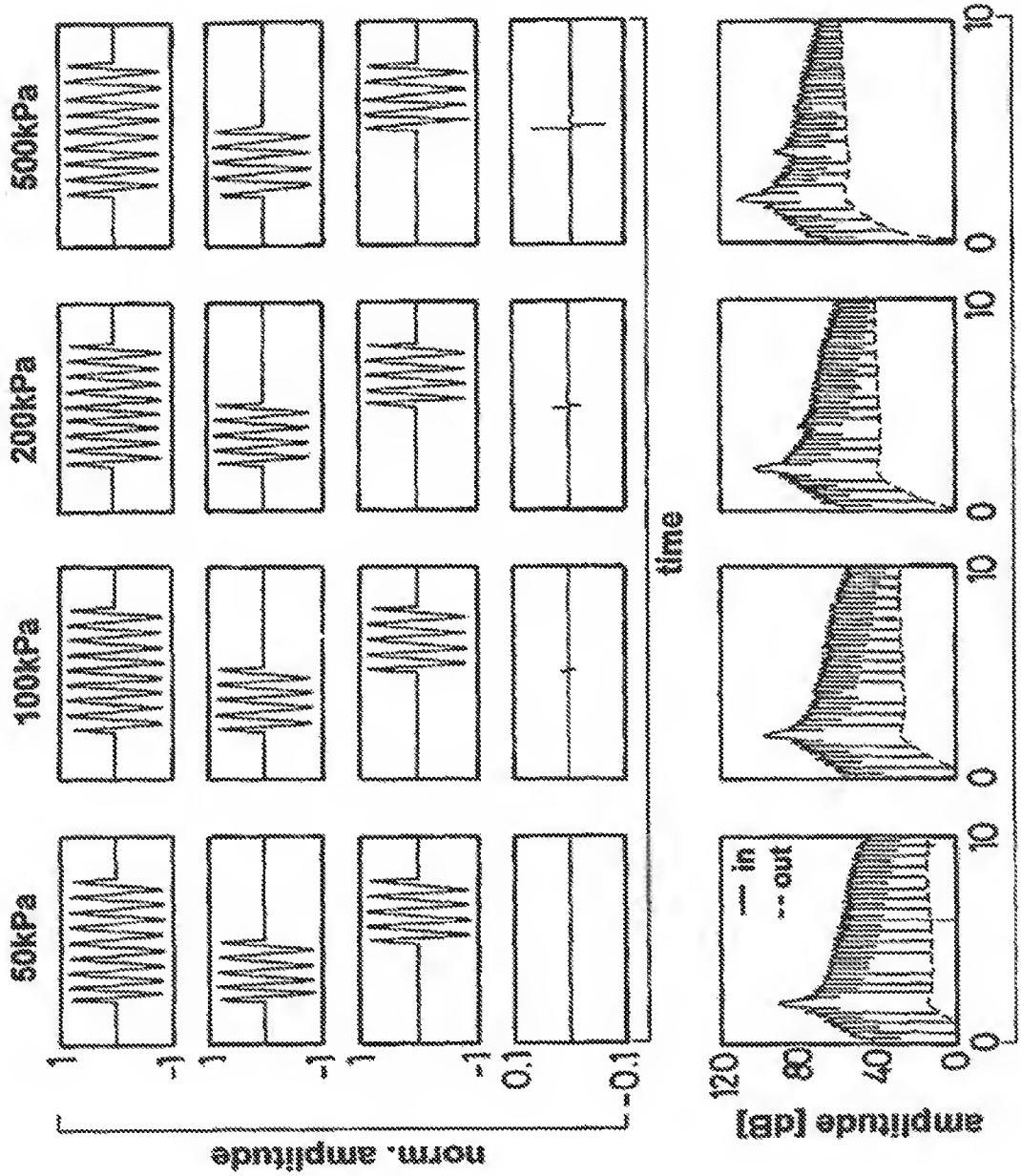


Fig. 3(b)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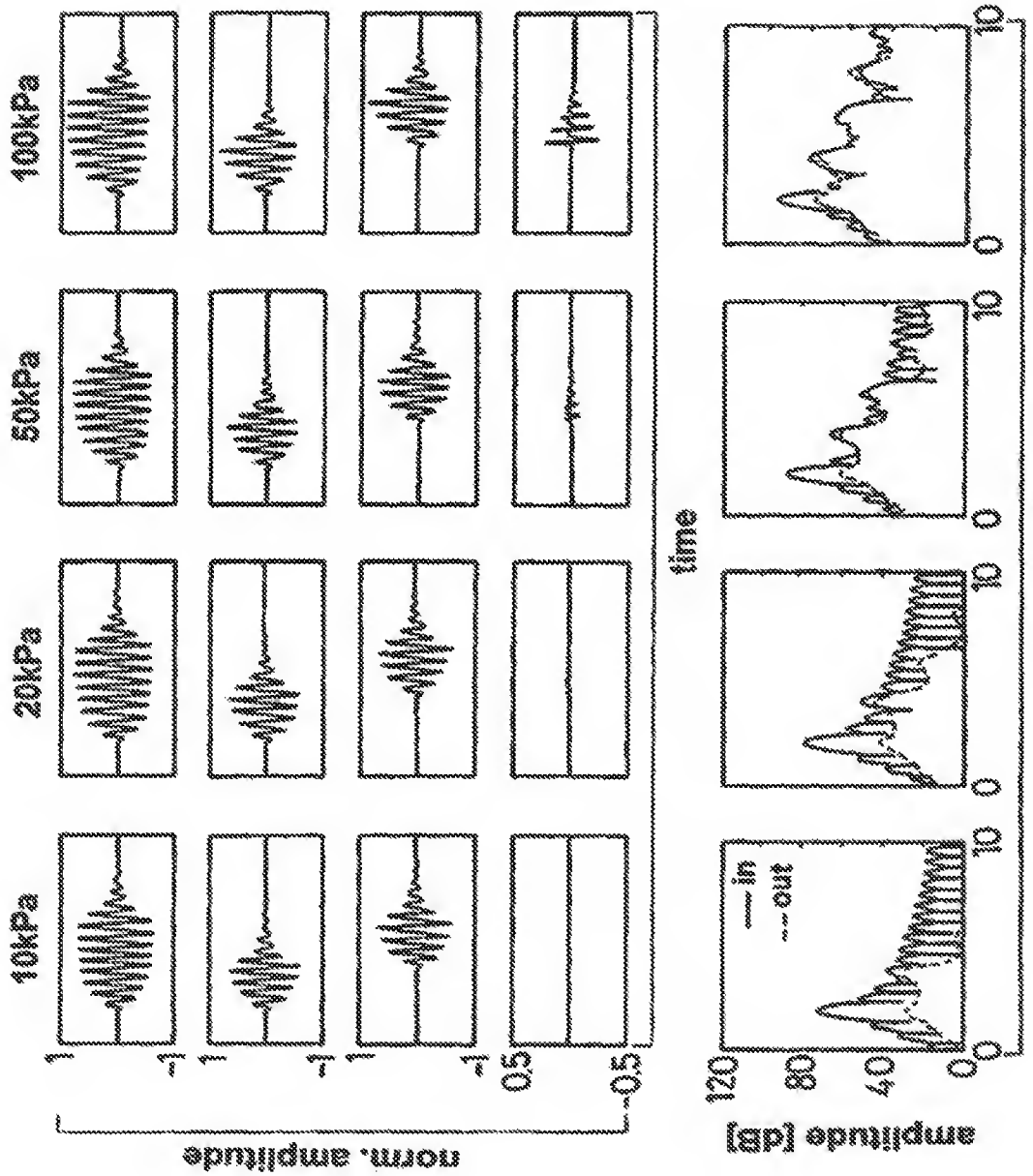
100kPa
200kPa
500kPa
norm. amplitude
time
amplitude [dB]
frequency [MHz]
— in
-- out

Fig. 4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100kPa
norm. amplitude
time
amplitude [dB]
frequency [MHz]
in
out

Fig. 5

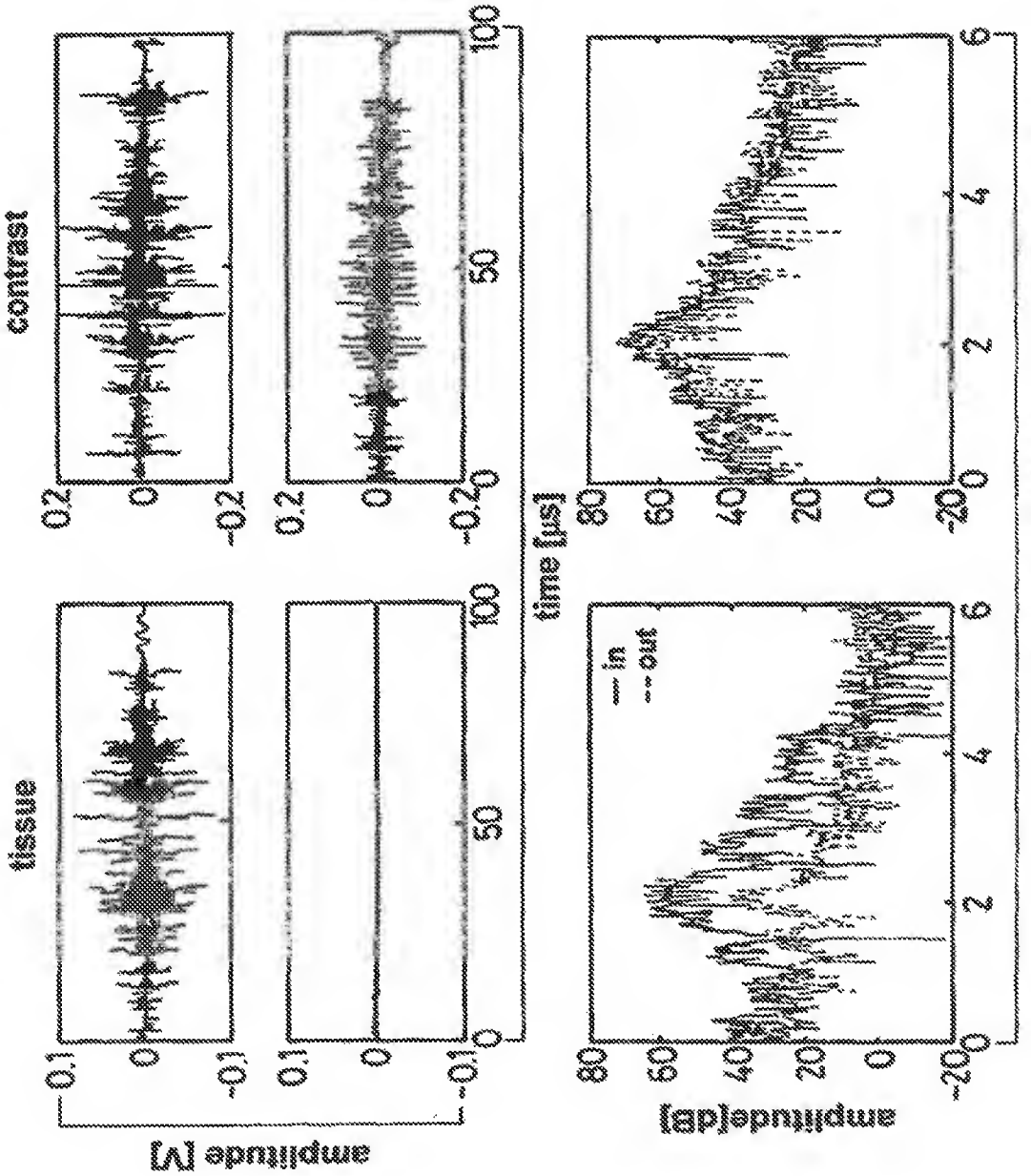
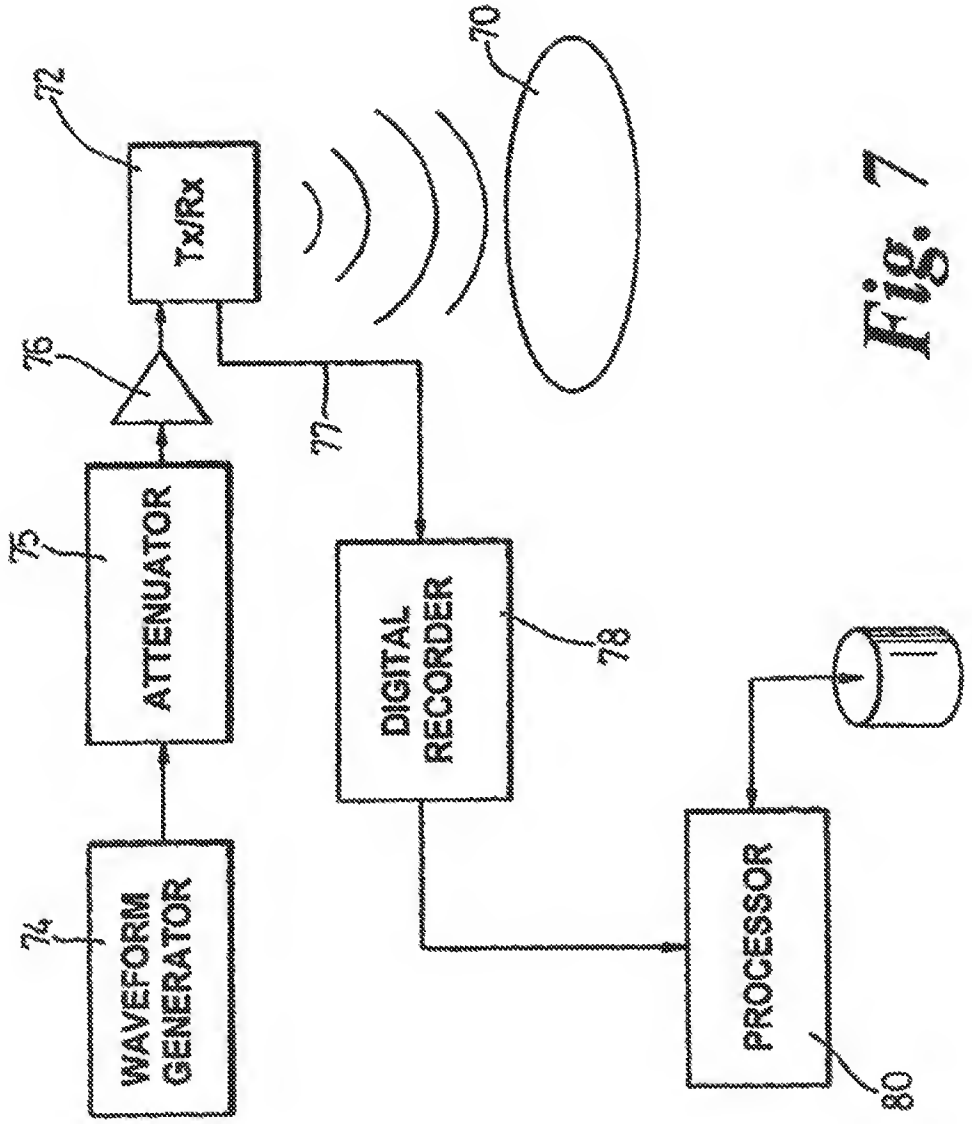

tissue
contrast
amplitude [V]
time [µs]
frequency [MHz]
amplitude[dB]
— in
-- out

Fig. 6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72
Tx/Rx
76
77
75
ATTENUATOR
DIGITAL RECORDER
78
74
WAVEFORM GENERATOR
PROCESSOR
80

Fig. 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/009046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B8/00 G01S7/52 G01S15/89

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B G01S

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 095 621 A (MATSUSHITA ELECTRIC INDUSTRIAL CO., LTD) 2 May 2001 (2001-05-02) paragraphs '0005!, '0007!, '0013!, '0016!, '0036!; figures 5a-5c	12,15, 22,26,27
A	BORSBOOM J ET AL INSTITUTE OF ELECTRICAL AND ELECTRONICS ENGINEERS: "Nonlinear coded excitation method for contrast imaging" 7 October 2001 (2001-10-07), 2001 IEEE ULTRASONICS SYMPOSIUM PROCEEDINGS. ATLANTA, GA, OCT. 7 - 10, 2001. IEEE ULTRASONICS SYMPOSIUM PROCEEDINGS, NEW YORK, NY : IEEE, US, PAGE(S) 1729-1732 , XP010584846 ISBN: 0-7803-7177-1 Section II and IV. figures 1,3	1-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2005	07/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kronberger, R

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/009046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2002/129656 A1 (TSUZUKI HIROHIKO) 19 September 2002 (2002-09-19) paragraphs '0001!, '0002!, '0035! - '0039!, '0045!, '0139! - '0147!, '0152!, '0169! - '0172!; figures 2,10	1-28
A	US 6 632 177 B1 (PHILLIPS PATRICK J ET AL) 14 October 2003 (2003-10-14) column 8, line 43 - column 11, line 24; figure 1 column 12, lines 21-65	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/009046

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EP 1095621 A	02-05-2001	DE 60016875 D1	27-01-2005
		JP 3300313 B2	08-07-2002
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US 6632177 B1	14-10-2003	NONE	